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Endurance exercise and atrial fibrillation

Atrial fibrillation among Norwegian veteran endurance athletes and the association between endurance exercise and risk of atrial fibrillation

Contents

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Abbreviations

AF = Atrial fibrillation

AFL = Atrial flutter

BMI = Body Mass Index

aOR = Adjusted odds ratio

aRD = Adjusted risk difference

CHD = Coronary heart disease

CI = 95% confidence interval

ECG = Electrocardiogram

HR = Hazard ratio

Kcal = Kilocalories

NYHA = New York Heart Association

OAC = Oral anticoagulant

OR = Odds ratio

PA = Physical activity

RD = Risk difference

RR = Relative risk

List of papers

I. **Increased risk of atrial fibrillation among elderly Norwegian men with a history of long-term endurance sport practice**
Myrstad M, Lochen ML, Graff-Iversen S, Gulsvik AK, Thelle DS, Stigum H, Ranhoff AH.
Scand J Med Sci Sports. 2014; 24, e238-e244.
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II. **Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter**
Myrstad M, Nystad W, Graff-Iversen S, Thelle DS, Stigum H, Aarønæs M, Ranhoff AH.
Am J Cardiol. 2014;114:1229-33.
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III. **Letter to the editor: Does endurance exercise cause atrial fibrillation in women?**
Myrstad M, Aarønæs M, Graff-Iversen S, Nystad W, Ranhoff AH.
Int J Cardiol. 2015;184:431-432.
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IV. **Physical activity, symptoms, medication and subjective health among veteran endurance athletes with atrial fibrillation**
Myrstad M, Aarønæs M, Graff-Iversen S, Ariansen I, Nystad W, Ranhoff AH.
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Summary

Background

Atrial fibrillation (AF) is the most common clinically relevant cardiac arrhythmia. AF is associated with reduced functional capacity and other symptoms, drug use, poor subjective health, increased risk of ischemic stroke and increased mortality.

Physical activity (PA) reduces the risk of cardiovascular diseases and have multiple beneficial health effects, but male endurance athletes seem to have an increased risk of AF. Few studies, however, have investigated the association between prolonged endurance exercise and the risk of AF, and this association has not been studied in women previously. The number of individuals aged >40 years that engage in endurance sports events is increasing, but few studies have investigated the association between endurance sport practice and risk of AF in veteran athletes. Furthermore, AF and its consequences have been just sporadically described in veteran athletes previously.

The main aims of this thesis were 1) to investigate endurance sport practice as a risk factor for AF in veteran athletes (paper I), 2) to investigate the association between prolonged regular endurance exercise and risk of AF in men (paper II), 3) to investigate the association between prolonged regular endurance exercise and risk of AF in women (paper III), and 4) to characterize AF and investigate PA, endurance exercise, symptoms, drug use and subjective health in veteran athletes with AF (paper IV).

Methods

Paper I is based on the Birkebeiner Ageing Study. In this cross-sectional study, 509 out of 607 invited men (84%) aged ≥65 years who took part in the 54-kilometer Birkebeiner cross-country ski race in 2009 or 2010 participated. These veteran athletes were compared to 1768 out of 2757 invited men aged ≥65 years (68%) participating in a population-based health study. The main outcome AF was self-reported by questionnaires. The main exposure was endurance sport practice, defined as participating in the Birkebeiner race. We calculated adjusted risk differences (aRDs) for AF with 95% confidence intervals (CIs) using a linear regression model.

In the papers II and III, we investigated the association between prolonged regular endurance exercise and the risk of AF in men and women, respectively. These papers are based on a second study, the Birkebeiner Atrial Fibrillation Study. The study population of this retrospective cohort study comprised two distinct cohorts: 1) Veteran athletes aged ≥53 years who had participated in the Birkebeiner race in 1999, and 2) Participants in the same group in a population-based health study. In total, 5390 out of 7500 invited men and women (72%) took part in the Birkebeiner Atrial Fibrillation Study. In the study of men (paper II), the main outcome was AF and atrial flutter (AFL) confirmed by electrocardiograms (ECGs) in a review of medical records. Due to the low

number of confirmed AF cases among female participants, self-reported AF was the main outcome in the analysis of women (paper III). The main exposure, years of regular endurance exercise was self-reported by questionnaires. Regular endurance exercise was defined as exercise for at least 30 minutes ≥3 times per week with the purpose of increasing physical endurance capacity. Adjusted odds ratios (aORs) for AF with CIs were calculated using weighted logistic regression models.

Also paper IV is based on the Birkebeiner Atrial Fibrillation Study. In this study, we characterized AF in detail among 140 veteran skiers and 118 individuals from the general population with confirmed AF. Furthermore, we investigated engagement in PA and endurance exercise after the onset of AF, palpitations, functional capacity, drug-use and subjective health in veteran athletes with AF and in the general AF population.

Results

The prevalence of self-reported AF in the Birkebeiner Ageing Study was 13.2% in the veteran athletes and 11.6% in the men from the general population. After multivariable adjustment for age, height, body mass index (BMI), coronary heart disease (CHD), hypertension, diabetes mellitus, smoking, alcohol consumption, leisure-time PA during the past year and education, endurance sport practice was associated with an added risk of AF of 6 percent points (pp) (aRD 6.0 (CI 0.8-11.1)), corresponding to an aOR of 1.90 (CI 1.14-3.18).

In the Birkebeiner Atrial Fibrillation Study, the prevalence of self-reported AF was 12.5% among the male veteran athletes. After multivariable adjustment for age, height, concomitant heart disease, hypertension, diabetes mellitus and cohort affiliation, years of regular endurance exercise was associated with a gradually increased risk of both AF and AFL. Per 10 years of exercise, the aOR was 1.16 (CI 1.06-1.29) for AF and 1.42 (CI 1.20-1.69) for AFL. In stratified analyses, the associations were significant both in the veteran athletes and in the men from the general population. Men who had exercised regularly for ≥40 years had an aOR for AF of 1.94 (CI 1.19-3.14)) compared to men who had never exercised regularly.

The prevalence of self-reported AF among female veteran skiers was 8%. After multivariable adjustment for age, BMI, concomitant heart disease, hypertension, diabetes mellitus and cohort affiliation, women who had exercised regularly for ≥40 years had an increased risk of AF of borderline significance (aOR 2.18 (CI 0.94-5.06)) compared to women who had never exercised regularly.

Among veteran athletes with AF, 52% had paroxysmal, 23% had persistent and 24% had permanent AF. AF was associated with poor subjective health, but 89% of the veteran athletes were physically active and 64% engaged in regular endurance exercise after the onset of AF. While 59% had experienced palpitations during the past year, 32% reported reduced functional capacity. Two out of three with AF and an estimated CHA_2DS_2-VASc score ≥2 used oral anticoagulants (OACs).

Conclusions

In conclusion, 1) endurance sport practice seemed to be a risk factor for AF in men aged ≥65 years, 2) years of regular endurance exercise was associated with a gradually increased risk of both AF and AFL in men, 3) our study indicated that prolonged endurance exercise might be associated with AF also in women, and 4) AF was associated with poor subjective health, but the vast majority of veteran athletes engaged in regular PA and endurance exercise also after the onset of AF.

Norsk sammendrag

Innledning

Atrieflimmer (AF) er den vanligste hjerterytmeforstyrrelsen som har klinisk betydning. AF er forbundet med redusert fysisk yteevne og andre symptomer, medisinbruk, dårlig selvopplevd helse, økt risiko for hjerneslag og økt dødelighet.

Fysisk aktivitet (FA) reduserer risikoen for hjerte- og karsykdom og er forbundet med en rekke gunstige helseeffekter, men mannlige idrettsutøvere i utholdenhetsidretter ser ut til å ha en økt risiko for AF. Få studier har undersøkt sammenhengen mellom langvarig utholdenhetstrening og risiko for AF og tidligere studier har ikke funnet noen sammenheng mellom deltakelse i utholdenhetsidrett og risiko for AF blant kvinner. Stadig flere personer >40 år deltar i Birkebeinerrennet, maratonløp og lignende arrangementer, men FA og trening, symptomer, medisinbruk og selvopplevd helse blant eldre birkebeinere med AF har ikke blitt kartlagt tidligere.

Hensikten med studiene i denne avhandlingen var 1) å undersøke deltakelse i utholdenhetskonkurranser som risikofaktor for AF blant eldre birkebeinere(artikkel I), 2) å undersøke sammenhengen mellom langvarig regelmessig utholdenhetstrening og risiko for AF blant menn (artikkel II), 3) å undersøke sammenhengen mellom langvarig regelmessig utholdenhetstrening og risiko for AF blant kvinner (artikkel III), og 4) å beskrive AF og undersøke deltakelse i FA og utholdenhetstrening, symptomer, medisinbruk og selvopplevd helse blant eldre birkebeinere (personer ≥53 år som tidligere hadde deltatt i Birkebeinerennet (artikkel IV).

Metoder

Artikkel 1 er basert på Birkebeiner Aldringsstudien. Total 509 av 607 inviterte menn (84%) ≥65 år som var med i Birkebeinerrennet i 2009 eller 2010, deltok i denne tverrsnittsstudien. Birkebeinerne ble sammenlignet med 1768 av 2757 inviterte menn ≥65 år (68%) som hadde deltatt i en helseundersøkelsen i Tromsø (Tromsø-undersøkelsen). Studiens endepunktet var selv-rapportert AF og eksponeringen var deltakelse i Birkebeinerrennet. Justerte risikodifferanser (aRDs) med 95% konfidensintervaller (KIs) ble beregnet med en lineær regresjonsmodell.

I artikkel II undersøkte vi sammenhengen mellom langvarig regelmessig utholdenhetstrening og risiko for AF blant menn, og i artikkel III ble den samme sammenhengen undersøkt blant kvinner. Begge artiklene er basert på Birkebeiner Atrieflimmer Studien. Studiepopulasjonen i denne retrospektive kohortstudien er sammensatt av to uavhengige kohorter: 1) Menn og kvinner ≥53 år som deltok i Birkebeinerrennet i 1999, og 2) deltakere i en helseundersøkelse i Oslo (Oslo-undersøkelsen). Til sammen 5390 av de 7500 inviterte (72%) fra de to kohortene deltok i Birkebeiner Atrieflimmer Studien. AF og atrieflutter (AFL) bekreftet med elektrokardiogram under en gjennomgang av sykehusjournaler var hovedendepunktene i artikkel II. Fordi antallet kvinner med tilgjengelig journal var lavt, ble selv-rapportert AF valgt som endepunkt i studien av kvinner (artikkel III). Eksponeringen var selv-rapportert antall år med regelmessig utholdenhetstrening. Regelmessig utholdenhetstrening ble definert som utholdenhetstrening av minst 30 minutters varighet minst tre ganger i uken med mål om å forbedre utholdenhet. Justerte odds ratioer (aORs) med KIs ble beregnet med vektet logistisk regresjon.

Også artikkel IV er basert på Birkebeiner Atrieflimmer Studien. I denne artikkelen beskrev vi AF blant 140 birkebeinere og 118 personer fra den generelle befolkningen (Oslo-undersøkelsen) med bekreftet AF. Vi undersøkte også deltakelse i PA og utholdenhetstrening blant personer med AF, samt symptomer som hjertebank og redusert fysisk yteevne, medisinbruk og selvopplevd helse.

Resultater

Forekomsten av AF i Birkebeiner Aldringsstudien var 13.2% blant birkebeinerne og 11.6% i utvalget fra Tromsø-undersøkelsen. Etter justering for alder, kroppshøyde, kroppsmasseindeks (KMI), koronar hjertesykdom, høyt blodtrykk, diabetes mellitus, røyking, alkoholvaner, FA siste år og utdanningsnivå, var deltakelse i Birkebeinerrennet forbundet med et tillegg i risiko for AF på 6 prosentpoeng (pp) (aRD 6.0 (KI 0.8-11.1)). Dette tilsvarer en aOR på 1.90 (KI 1.14-3.18).

I Birkebeiner Atrieflimmer Studien var forekomsten av selv-rapportert AF blant de mannlige birkebeinerne 12.5%. Etter justering for alder, kroppshøyde, annen hjertesykdom, høyt blodtrykk, diabetes mellitus og kohort, var antall år med regelmessig utholdenhetstrening forbundet med en gradert økt risiko for både AF og AFL. Per tiår med trening var aOR 1.16 (KI 1.06-1.29) for AF og 1.42 (KI 1.20-1.69) for AFL. I stratifiserte analyser var sammenhengen signifikant både blant birkebeinerne og i utvalget fra Oslo-undersøkelsen. Menn som hadde trent regelmessig i ≥40 år hadde en aOR for AF på 1.94 (KI 1.19-3.14)) sammenlignet med menn som aldri hadde trent regelmessig.

Forekomsten av selv-rapportert AF blant de kvinnelige birkebeinerne var 8%. Etter justering for alder, KMI, annen hjertesykdom, høyt blodtrykk, diabetes mellitus og kohort, hadde kvinner som hadde trent regelmessig i ≥40 år en grensesignifikant forhøyet risiko for AF (aOR 2.18 (KI 0.94-5.06)) sammenlignet med kvinner som aldri hadde trent regelmessig.

Blant birkebeinerne med AF hadde 52% paroxysmal AF (anfall som går over av seg selv), 23% hadde persistent AF (anfall som går over etter behandling) og 24% permanent AF. AF var forbundet med dårlig selvopplevd helse, men 89% av birkebeinerne var fysisk aktive og 64% drev fortsatt med regelmessig utholdenhetstrening etter at de hadde fått AF. Mens 59% rapporterte å ha hatt hjertebank siste år, hadde 32% opplevd redusert fysisk yteevne. To av tre med AF og en estimert CHA_2DS_2-VASc ≥2 brukte orale antikoagulantia.

Konklusjoner

1) Deltakelse i Birkebeinerrennet så ut til å være en risikofaktor for AF blant menn ≥65 år, 2) antall år med regelmessig utholdenhetstrening var assosiert med en gradert økt risiko for både AF og AFL hos menn, 3) vår studie indikerte at langvarig utholdenhetstrening kan være forbundet med en økt risiko for AF også blant kvinner, og 4) AF var forbundet med dårlig selvopplevd helse, men majoriteten av birkebeinerne var regelmessig fysisk aktive og deltok i utholdenhetstrening også etter at de hadde fått AF.

1 Introduction

1.1 Physical activity and endurance exercise

1.1.1 Definitions

In terms of health-related research is *PA* defined as any bodily movement produced by skeletal muscles that results in energy expenditure [1]. The energy expenditure varies continuously from low to high and the lowest energy expenditure is seen during sedentary activities that involve sitting [2]. In research, PA is often categorized into occupational or leisure-time PA. Leisure-time PA covers households tasks like for example gardening, and recreational activities like cycling, walking and even regular exercise, and has traditionally been divided into 4 subcategories: Sedentary, light, moderate and high PA [3].

While PA covers bodily movement at any level, *exercise* is defined as planned, structured and repetitive bodily movement with the purpose to improve or maintain physical fitness [1]. The goal of *endurance exercise* is the improvement of physical capacity by increasing the maximum oxygen consumption. Endurance sports like cross-country skiing are characterized by a high dynamic component, defined in terms of a high achieved percent of maximal oxygen consumption and a high cardiac output during activity [4]. In this thesis, r*egular endurance exercise* has been defined as exercise for ≥30 minutes at least three times per week with the purpose of increasing physical endurance capacity. *Prolonged endurance exercise* is used to describe such exercise that has been continued for many years.

Over the last decades, there has been an increased participation in endurance sports events like marathons, triathlons and long-distance cross-country ski races [5, 6]. In this thesis the term *endurance sport practice* is used to describe participation in such endurance sports events.

There term *athlete* is widely used, but there is a lack of a clear-cut and uniform definition in previous studies [7]. *Former* or *veteran athletes* have previously been used to describe former top-level athletes aged 46-72 years [8, 9]. In this thesis we use the term *veteran athletes* to describe individuals who have participated in a long-distance cross-country ski race when aged ≥40 years.

1.1.2 Physical activity, endurance exercise and health outcomes

Already more than 2,000 years ago Hippocrates stated that "…the sick will of course profit to a great extent from gymnastics with regard to the restoration of their health, and the healthy will profit with regard to its maintenance, and those who exercise will profit with regard to the maintenance of their well-being and a lot more'' [10].

After the second world war, Jeremy N. Morris and his colleagues were the first to investigate the association between physical inactivity and risk of cardiovascular disease and death with modern epidemiological methods [11]. In a study conducted among >31 000 male employees of the London Transport Executive, Morris *et al,* demonstrated that the inactive drivers of the London buses had about the double age-adjusted rate of the conductors who ran up and down the stairs of the buses to sell tickets, of both fatal and non-fatal CHD. Since, knowledge regarding associations between PA and various health outcomes has been added and today PA and exercise are recognized as cornerstones of the primary prevention of many diseases and conditions. Reduced mortality is the best documented among the many beneficial health effects of PA [12-17], but also a reduced risk of cardiovascular diseases by regular PA is well established [18-24]. Furthermore, PA reduces the risk of stroke and cardiovascular risk factors like hypertension, diabetes mellitus and obesity [25-33], and a reduced risk of cancer by PA has been demonstrated [34-38].

Because the prevalence of risk factors increases with increasing age, the potential benefits of PA and exercise might be highest in the oldest age groups. In a recent Norwegian study, the relative importance of PA as health promoting factor increased with increasing age, when compared to other cardiovascular risk factors [39]. Improved cognitive functions and reduced risk of dementia, reduced risk of depression, increased muscle strength and volume, improved mobility, increased bone density, and reduced risk of falls and fractures are among other benefits of PA observed in studies of old individuals [40, 41].

Finally, although rest was recommended for patients with established CHD for decades, exercise is today the most important component of cardiac rehabilitation and secondary prevention of many diseases [42, 43].

It seems to be an inverse dose-response relationship between PA and health outcomes: Increased levels of PA are associated with lower mortality and morbidity [44]. The largest improvement might be achieved by moving from inactive to active, while less benefit could be expected by increasing the activity level from moderate to high [45]. However, also endurance exercise is associated with reduced mortality [46-49]. In a recently published study among >44,000 men in the United States, increasing amounts of high PA remained inversely associated with the risk of cardiovascular and other diseases, even among the men in the highest categories of exercise [50]. Also elite athletes have lower mortality rates than the general population [51]. On the other hand, in a cohort study of Dutch male non-elite participants in a long-distance speed skating event, the mortality was lower among those who participated in the recreational tour compared to those who competed in the race [49]. Recently, a Danish study suggested a U-shaped association between dose of jogging and mortality [52]. Thus, the optimal dose of exercise in terms of health promotion is controversial, and there is a need for studies that include individuals exposed to various levels of exercise [53].

1.1.3 Adverse effects of endurance exercise and sport practice

In general, exercise has few harmful side-effects. Some activities like alpine skiing, bike cycling, boxing and other contact sports are related to an increased risk of traumatic injuries, and running frequently cause musculoskeletal overuse-injuries [54]. But most sports injuries are minor and have relatively little impact on the general health condition. However, it is well known that endurance sport practice might induce life-threatening ventricular arrhythmias and sudden cardiac death in individuals with pre-disposition [55-57]. In a Swedish study, cross-country skiers participating in the 90-kilometer Vasaloppet had an increased risk of acute mortality during the race, but the authors of the paper concluded that this risk was by far outweighed by the long-term protective effects on mortality of PA and exercise [48].

1.2 Atrial fibrillation

1.2.1 Definition, classification natural course

AF was first described in humans by Einthoven in 1906 [58]. AF is the most common sustained cardiac arrhythmia and characterized by absolutely irregular RR intervals in the ECG. The precise underlying mechanisms are still under debate [59], but the arrhythmia is mainly initiated by triggers located in the pulmonary veins and maintained due to micro-circuits of electrical waves, usually referred to as micro-re-entries or rotors [60]. AF is usually classified into three or five subtypes. In clinical practice in Norway three subtypes are commonly used:

1) Paroxysmal - self-terminating AF, usually within 48 h.
2) Persistent - AF episodes that either lasts longer than 7 days or requires termination by cardioversion with drugs or by direct current cardioversion.
3) Permanent – AF is present permanently.

In addition, the 2012 focused update of the European Society of Cardiology (ESC) guidelines recommend to use two other subtypes [61]:

4) First-time diagnosed AF, and
5) Long-lasting persistent AF that has lasted for >1 year.

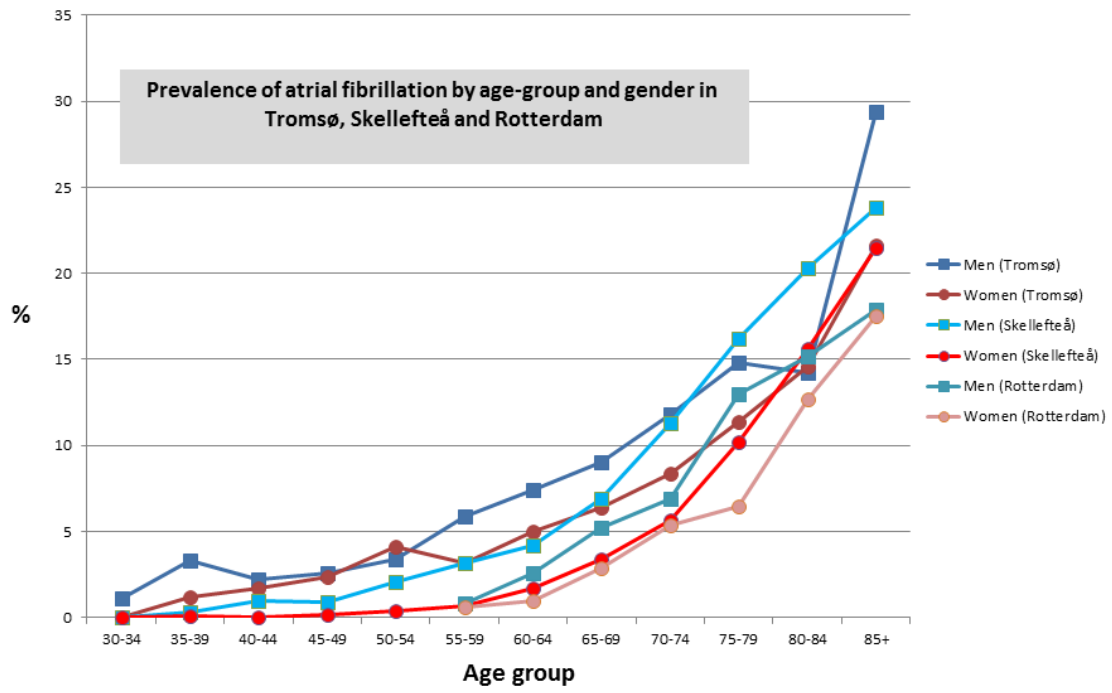
The natural course of the arrhythmia is a progression from short and rare episodes to longer lasting and more frequent attacks. AF paroxysms vary over time and between individuals, both in terms of frequency, duration and symptoms. Only 2-3% of all AF patients remain with paroxysmal AF over time [62], and AF typically develop into a more permanent arrhythmia with increasing age. Thus, the proportions of the AF subtypes vary dependent on the studied population. In a prevalence study among 75-years old Norwegians, 11% of the individuals with AF had first-time diagnosed AF, 36% had paroxysmal, 1% had persistent and 52% had permanent AF [63].

1.2.2 Epidemiology

The overall prevalence of AF in the general western population is 1-2 %, but the prevalence increases with increasing age [64]. The prevalence is less than 0.5% before the age of 50 years, but increases steeply from the age of around 60 to 65 to around 10% in men and women aged 70-75 years, and more than 15% in those aged over 80 years [65, 66]. Figure 1 shows the prevalence of AF by age group in men and women in three population-based studies conducted in Tromsø, Skellefteå (Northern Sweden) and Rotterdam. The prevalence was highest in the Tromsø study, were AF was self-reported (unpublished data). Similar to CHD [67], AF seems to occur 5-10 years later in women than in men. The prevalence was higher in the Swedish study from 2010 compared to the Rotterdam study conducted around 20 years earlier. Due to increased survival after acute coronary syndrome, increased prevalence of risk factors for AF like obesity and diabetes and the ageing population, the prevalence of AF might be increasing over time, with estimates indicating a doubled prevalence within the next 50 years [64, 68].

There are no complete AF prevalence data available for the Norwegian population. Tveit, *et al,* found a prevalence of 10% in a population of 75-years old Norwegians , 6% in women and 15% in men [63]. In 2011, Tveit estimated that 73,500 Norwegians had AF and that the prevalence is likely to be doubled until 2040 [69].

Figure 1. Prevalence of atrial fibrillation by age group and gender in Tromsø (2007-08) (unpublished data), Skellefteå (Northern Sweden) (2010) and Rotterdam (1990-93), modified [65, 66].



1.2.3 Symptoms

The most commonly reported symptom among AF patients is palpitations [70]. In this thesis, *palpitations* are defined as sudden changes in the heart rate or heart rhythm that are perceived by the patient. Other commonly reported symptoms are dyspnea, chest pain, dizziness, fatigue, anxiety, exercise intolerance and reduced functional capacity [70]. In this thesis, *reduced functional capacity* is defined as limitations in physical functions due to symptoms like dyspnea, chest pain or fatigue related to the heart disease, as measured by the New York Heart Association (NYHA) classification. Furthermore, AF is related to poor subjective health and drug use [71, 72]. In previous studies, patients with paroxysmal AF were more likely to be symptomatic than patients with permanent AF [72]. Symptoms in AF patients might be caused by the arrhythmia itself or by concomitant conditions. As heart failure, CHD, heart valve diseases and other co-morbidities are common in AF patients, the causes of symptoms are probably multifactorial in many individuals [70]. The symptom burden is therefore likely to vary dependent on the studied population.

1.2.4 Consequences

AF is associated with increased risk of all-cause mortality, stroke and heart failure [73]. In the Framingham Study, AF was associated with an aOR of death of 1.5 (CI 1.2 – 1.8) [74], and among Swedish AF patients, the standardized mortality ratio was 1.6 (CI 1.4 – 1.8) compared to the general population [75]. In this study, the increased mortality appeared to be related to concomitant cardiovascular risk factors, but in another Swedish study, AF was found to be an independent risk factor for mortality, even after adjustment for co-morbidity [76]. In another study, the relative risk (RR) for death in individuals with AF was higher in women than in men (RR 2.2 versus 1.5) [73].

In a population of >186,000 AF patients with a mean age of 79.5 years and a high prevalence of co-morbid conditions, death was the most frequent major outcome within the first five years after the diagnosis of AF [77]. The cumulative incidence of death was 19.5% after 1 year and 48.8% after 5 years. After 5 years of follow-up, 13.7% of the patients had a hospitalization or emergency department visit for heart failure, 7.1% developed stroke, 5.7% had a gastrointestinal bleeding and 3.9% had a myocardial infarction.

The overall risk of stroke is around five times higher among AF patients compared to the general population [78]. While paroxysmal AF seems to carry the same risk as permanent AF [75], the risk of stroke depends upon age, sex and concomitant risk factors [79-81]. Cardiac failure or dysfunction, hypertension, age ≥75 years (≥65 years), diabetes mellitus, previous stroke, other vascular disease and female gender have been identified as important risk factors for stroke in AF patients and are implemented in the modified CHA_2DS_2-VASc-score, that has been recommended in the decision-making about OAC treatment in order to prevent stroke in AF patients [61, 82]. The increased risks of both death and stroke are reduced by OAC [61, 64, 75, 83], but the adherence to OAC treatment has been found unsatisfactory in previous studies [84-86].

1.2.5 Etiology and risk factors

Although the understanding of the etiology of AF is still incomplete, a broad spectrum of risk factors has been associated with AF during the last decades. Recently, several papers divided these into conventional or validated risk factors that are well documented, and less established, less validated, newer or emerging risk factors [87-89]. Risk factors for AF based on recent reviews are summarized in table 1. Endurance sport practice and endurance exercise are listed among the less established risk factors for AF.

Table 1. Established and less established risk factors for atrial fibrillation, based on recent reviews[a] [87-89].

Established risk factors	Less established risk factors
Advancing age	Obesity
Male gender	Body height
Hypertension	Obstructive sleep apnea syndrome
Coronary heart disease	Chronic obstructive pulmonary disease
Valvular heart disease	Chronic kidney disease
Heart failure	Subclinical hyperthyroidism
Diabetes mellitus	Excessive alcohol consumption
Hyperthyroidism	Smoking
Genetic factors	Coffee
	(Biomarkers of) inflammation (CRP, TNF-alfa, IL6)
	Biomarkers of hemodynamics stress (ANP, BNP)
	Biomarkers of cardiac damage (Troponin T)
	Prolonged endurance exercise
	Endurance sport practice
	Murmur
	Pre-clinical atherosclerosis
	Birth weight >4 kg
	Psychological determinants (stress, anger, hostility)
	Left atrial dilatation
	Left ventricular hypertrophy
	Diastolic dysfunction
	Atrial conduction delay (PR-interval)

[a] The list is not necessarily exhaustive.

Historically, the term *lone AF* has been used to describe AF in younger individuals without any other cardiovascular disease or other detectable relevant co-morbidity. However, the long list of emerging risk factors has raised the question whether lone AF does exist, and if the term should be avoided [88].

1.2.6 Atrial flutter

AFL is an atrial arrhythmia closely related to AF. AFL is the second most common clinically relevant arrhythmia, but its prevalence is less than one tenth of that of AF [90]. Also AFL is strongly related to increasing age, most often occurs in relation to co-morbid conditions and is associated with the same long-term consequences as AF [91]. As in AF, AFL is also often characterized by an increased heart rate, but unlike AF, the heart rate is regular.

1.3 Endurance exercise, sport practice and risk of atrial fibrillation

1.3.1 Previous studies of Norwegian cross-country skiers

Already in 1978 Lie and Erikssen showed that ECG abnormalities were frequent in male Norwegian cross-country skiers participating in the Birkebeiner race [92]. After five years follow-up, they concluded that the abnormalities probably were explained by physiological adaption to exercise, and that exercise seemed to protect against CHD [93]. In the BirkOpp-study, Grimsmo, *et al*, studied morbidity and mortality in a 28-30-years follow-up of 78 of the same skiers. The skiers were aged 54-92 years at follow-up and had a high overall prevalence of AF of 16.7%. The prevalence of lone AF was 12.8 % [94]. Echocardiographic evaluation revealed that a high proportion of the skiers had enlarged left atrium dimensions. Long PQ time, bradycardia and left atrial enlargement were predictors for AF in this study [95]. The mortality was lower in the skiers compared to the general population [96]. Sivertsen, *et al,* studied 24 cross-country skiers who had been part of the Norwegian national team 25 years after their active competing period [97]. The main result of this study was that the athletes had maintained their physical capacity well after concluding their careers. Two athletes developed paroxysmal AF during the follow-up. In another study, Bjørnstad, *et al*, followed 30 Norwegian elite endurance athletes for 15 years [98]. All 30 had ended their professional careers, but were still engaged in recreational activities. There were no cases of AF, AFL or other clinical events during the follow-up.

1.3.2 Previous studies of atrial fibrillation in athletes

In 1998, Karjalainen, *et al*, were the first to describe an association between endurance sport practice and AF [8]. Finnish male elite orientation runners aged 35 to 59 years at inclusion were compared with healthy men of the same age and followed-up for ten years. Individuals with incident cardiovascular diseases during the follow-up were excluded. The prevalence of lone AF was five-fold higher in the orientation runners than in the control group (OR 5.5 (CI 1.3 – 24.4)). The main strengths of this study were the long follow-up and that also mortality and cardiovascular diseases were recorded. The study was limited by a low AF incidence and a twice as high number of drop-outs in the control group compared to the athletes. Interestingly, when analyzing the data without excluding those with incident cardiovascular diseases others than AF, there were no significant difference in the AF incidence between the groups [99]. Since 1998, atrial arrhythmias have been studied in other populations of athletes. Studies published until 2012 are summarized in table 2.

Table 2. Studies of atrial fibrillation in athletes published until 2012.

Study	Study design and population(s)	AF cases	Risk estimates	Comments
Sivertsen, 1994 [97]	Cohort study, 24 Norwegian elite cross-country skiers, 25 years follow-up, no control group	2	-	1 death due to myocardial infarction.
Karjalainen, 1998 [8]	Cohort study, 262 Finnish elite orientation runners vs. healthy recruits, 10 years follow-up	12 athletes, 2 controls	Lone AF: OR 5.5, CI 1.3 – 24.4	Higher number of drop-outs in the control group.
Molina, 2008 [100]	Retrospective cohort study, 252 Spanish non-elite marathon runners vs. sedative controls	9 runners, 2 controls	HR 8.8 (CI 1.3-61.3)	Shorter follow-up period in the control group (6 vs. 11 years). 44% smokers.
Baldesberger, 2008 [9]	Retrospective cohort study, 62 Italian former professional cyclists vs. golf players, mean follow-up 38 years	2 AF, 4 AFL, none in controls	-	71% admitted use of doping. High prevalence of CHD and hypertension
Bjørnstad, 2009 [98]	Cohort study, 30 Norwegian elite endurance athletes, no control group	None	-	
Grimsmo, 2010 [94]	Cohort study, 78 Norwegian veteran cross-country skiers, 28-30 years follow-up, no control group	13 (16.7%)	-	Prevalence of lone AF 12.8%.
Pellicia, 2010 [101]	Cohort study, young Italian elite athletes, mean follow-up 8.6 years, no control group	None	-	Mean age 22 at inclusion.
Van Buuren, 2012 [102]	Cross-sectional study, 33 former top-level German handball players	10	-	Selection of athletes with symptoms.

AF = Atrial fibrillation. AFL = Atrial flutter. CHD = Coronary heart disease. OR = Odds ratio. HR = Hazard ratio.

A common limitation of all these studies is the low number of AF cases. Another important limitation of many studies is the inadequate controlling for confounding factors. Despite a high prevalence of smokers among the Spanish marathon runners, only age and hypertension were included in the regression model [100]. Among the Italian cyclist, 44 out of 62 reported use of amphetamine or anabolic steroids [9]. The prevalence of AF is very low in young populations, and this is the most likely explanation for the negative results of the studies conducted in young Italian and Norwegian elite athletes [97, 101].

1.3.3 Previous studies of the association between endurance exercise and the risk of atrial fibrillation

One study prospectively investigated the risk of AF by endurance exercise in a larger population. In the Physicians Health Study, 16,921 healthy male doctors aged 40-84 years were followed for 12 years [103]. Both exercise and AF were self-reported by questionnaires and 1661 men reported AF during the follow-up. A modestly increased risk for AF was found among the most active physicians who reported five to seven weekly hours of exercise (aRR 1.20 (CI 1.02 – 1.41)) In subgroup analyses, the AF risk was increased only in men aged <50 years who exercised five to seven days per week, and jogging was the only type of activity associated with AF. The self-reporting of both the exposure and the outcome is the main limitation of this study. Furthermore, its generalizability is uncertain, because healthy physicians represent a selected population that might report both exercise and health outcomes differently from other populations.

A group of sports cardiologists in Barcelona has studied sport practice among patients with lone AF attending their outpatient arrhythmia clinic. Among 1160 patients consecutively referred to this clinic, 51 men aged ≤65 years with lone AF were identified. 63% of the men with lone AF were sportsmen, compared to 15% in the general Catalonian population [104]. The same 51 men were included in a case-control study conducted and compared to 109 controls from the general population. In this analysis, current sport practice combined with >1500 lifetime hours of self-reported sport practice was associated with an OR for lone AF of 2.87 (CI 1.20-6.91). The authors suggested a threshold of 1500 hours of sport practice than must be exceeded to facilitate AF [105]. In a third study, the Barcelona group demonstrated that PA, body height and left atrial size predicted lone AF [106]. This was a prospective case-control study of 107 patients with lone AF and 107 age- and sex-matched controls, and is interesting because both occupational PA and exercise and sports activity were assessed using a detailed questionnaire. All activities were categorized by intensity, but unfortunately and probably due to the small study size, both occupational PA and exercise were analyzed together in the multivariable regression analysis. This implies that occupational PA of high intensity was classified together with for instance competitive sport practice. The CIs were wide and overlapping between the categories of activity and the study was not able to demonstrate a dose-response relationship. A main limitation of all three studies might be that the outpatient arrhythmia clinic in Barcelona is known for its expertise in sports cardiology, which is likely to have introduced selection bias.

1.3.4 Meta-analysis and reviews

In 2009, six case-control studies with a total of 655 athletes and 895 controls were included in a meta-analysis. The overall risk of AF was found to be significantly higher in the group of athletes than in the controls, with an OR for AF of 5.3 (CI 3.6 – 7.9) [107].

In 2012, we published a review article including both the meta-analysis and previous studies and concluded that the literature provided support for an increased risk of AF related to prolonged endurance exercise [108]. We discussed a number of important limitations: Two of the studies were based on the same patient material [104, 105], which might raise the suspicion of publication bias and an overestimation of the studied association. Most studies were likely to be affected by selection bias [8, 9, 100, 103, 105, 106, 109], and some studies had a high risk of information bias, because the registration of the endpoint could be associated with the studied exposure [105, 106]. Finally, we highlighted the lack of controlling for confounding factors in some studies [8, 103, 110].

Until 2012, several reviews were published, including largely the same studies as we did. Three reviews were published by Mont or others from the Barcelona group and concluded that growing evidence supports that prolonged endurance sport participation can cause cardiac structural changes and alterations in the autonomic system, which can facilitate atrial arrhythmias [111-113]. Sorokin, *et al,* concluded that evidence support that athletes are at increased risk of AF [114]. Turagam, *et al,* concluded that the prevalence of AF seemed to be higher in individuals involved in prolonged sport practice compared to general populations, but that evidence for a causal relation between sport practice and risk of AF was lacking [115]. On the other hand, Delise, *et al,* stated that there is no convincing data that sport itself may be the cause of AF and that a possible facilitating effect on AF is limited to vigorous endurance exercise [99]. Also Müller-Riemenschneider, *et al,* concluded that the quality of evidence for an increased risk of AF by exercise was low, and that the risk most likely is overestimated in most studies [116].

1.3.5 Summary of previous studies

Thus, the results of a few studies indicated a high prevalence of AF in athletes and an association between endurance sport practice and an increased risk of AF. With exception from the Physicians Health Study, which was conducted in a selected population of physicians, AF risk had only been studied in relatively small samples of men. Grimsmo, *et al*, had studied prolonged endurance sport practice among Norwegian veteran cross-country skiers, but without any control group. A common limitation of all previous studies was the lack of data on the association between exercise and AF in women.

2 Aims of this thesis

Based on the knowledge gap regarding the association between prolonged endurance sport practice and exercise and the risk of AF, the following main aims emerged for this thesis:

I. To investigate endurance sport practice as a risk factor for AF in veteran athletes (Paper I)

II. To investigate the association between prolonged regular endurance exercise and risk of AF in men (Paper II)

III. To investigate the association between prolonged regular endurance exercise and risk of AF in women (Paper III)

IV. To characterize AF and to investigate PA, endurance exercise, symptoms, drug use and subjective health among veteran cross-country skiers with AF (Paper IV)

3 Materials

3.1 The Birkebeiner cross-country ski race

The Birkebeiner race has been arranged almost annually since 1932 [117]. The race was initiated to honor the rescue of the 18 months old Norwegian Prince Haakon Haakonsen in 1206. After the death of King Haakon Sverreson, the rivaling fractions the Baglers and *the Birkebeiners* were fighting to gain control over Norway. With the aim of securing the throne, a group of Birkebeiners took care of king Haakon Sverresons son Haakon and protected him against the Baglers. On their way to Trondheim, the Birkebeiners chose the strenuous route across the mountains separating Gudbrandsdalen and Østerdalen, and the two best skiers among them carried the small prince. Haakon Haakonson grew to become the king who later united Norway after 1000 years of sivil war [118]. The name Birkebeiner referred to leggings of birch bark and was given by the Baglers to describe their enemies as poor and incapable. Since the Birkebeiners proved the the Baglers to be wrong, their name was later related to strength, endurance and pride. Today the word *birkebeiner* is commonly used to describe participants of the Birkebeiner race [118].

Starting in Rena in Østerdalen and finishing in Lillehammer, the host city of the Olympic winter games of 1994, in Gudbrandsdalen, the course of the race is today 54 kilometers. With a total of about 1000 uphill altitude meters and often though weather conditions, the Birkebeiner race is among the world's most challenging cross-country ski races. All participants have to carry a backpack of at least 3.5 kg, representing the weight of prince Haakon. While 147 men completed the very first race in 1932, today the race is among the most popular sport events in Norway, and around 15,000 men and women participate every year [117].

3.2 The Birkebeiner Ageing Study

The study population of paper I is based upon 1) a cohort of male veteran cross-country skiers aged ≥65 who participated in the Birkebeiner Ageing Study, and 2) a cohort of men of the same age group participating in the population-based Tromsø Study.

3.2.1 The Birkebeiner Ageing Study

The Birkebeiner Ageing Study is a longitudinal study of veteran skiers participating in the Birkebeiner race. The main purpose of this study is to investigate associations between endurance sport practice and health in advanced age. Based on result lists provided by the race organizer, all 658 Norwegian skiers aged ≥65 years who completed the race in 2009 or 2010 and had a Norwegian postal address were invited to participate.

The inclusion of participants to the Birkebeiner Ageing Study took place in 2009 and 2010. Altogether, 484 participants in Birkebeinerrennet 2009 received a postal questionnaire together with an invitation letter during October the same year. During December, 116 individuals who had not responded to this invitation received a postal reminder. Correspondingly, 174 participants in Birkebeinerrennet 2010 who were not already included in the study received the questionnaire and invitation letter during November 2010. In total, 90 individuals were reminded by e-mail during January 2011, using e-mail addresses provided by the Birkebeiner race organizer. This, however, was not successful, as many participants were registered with the e-mail address of family members or others. Therefore, 50 individuals were also reminded by a telephone call.

Due to low number of female participants, only men were included in the analysis of this work. All male responders, 509 out of 607 invited men (84%) aged 65 to 90 years, were included. In order to investigate endurance sport practice as a risk factor for AF, cross-sectional baseline data from the Birkebeiner Ageing Study were compared with data from the sixth survey of the Tromsø Study (Tromsø 6).

3.2.2 The Tromsø Study

The Tromsø Study is a population-based general health study in the largest city in Northern Norway [119]. Since the study was initiated in 1974, repeated cross-sectional surveys have been carried out. Tromsø 6 took place in 2007-2008. In this survey, 19,762 inhabitants in Tromsø aged ≥30 years were invited to participate. In the age group 60-87, all inhabitants were invited. In total, 12,984 men and women participated (66%). The response rate was highest among men aged 65-69 (78%) and lowest among the oldest men aged ≥85 (28%) [120]. In this work, 1768 out of 2757 invited men aged 65 to 87 years (68%) were included.

3.3 The Birkebeiner Atrial Fibrillation Study

As the Birkebeiner Ageing Study was not originally designed to study AF, to further investigate the association between prolonged endurance exercise and risk of AF, a second study was designed: The Birkebeiner Atrial Fibrillation Study. The papers II, III and IV are based upon this study. Figure 2 illustrates the inclusion process of the Birkebeiner Atrial Fibrillation Study. The study population of this study comprises two distinct cohorts: 1) A cohort of veteran cross-country skiers aged ≥53 years who had been participating in the Birkebeiner race (different from the cohort of the Birkebeiner Ageing Study), and 2) a subset of participants in the population-based Oslo Health Study.

During June 2012, all 7500 invitees in the Birkebeiner Atrial Fibrillation Study received a questionnaire together with an invitation letter. The questionnaire was identical for all participants, regardless of which cohort they were recruited from. A first reminder was sent out to 3505 non-responders during September the same year. In addition, 888 individuals who had filled out and sent in the questionnaire but not completed the consent form were reminded. A second reminder was sent out during December 2012.

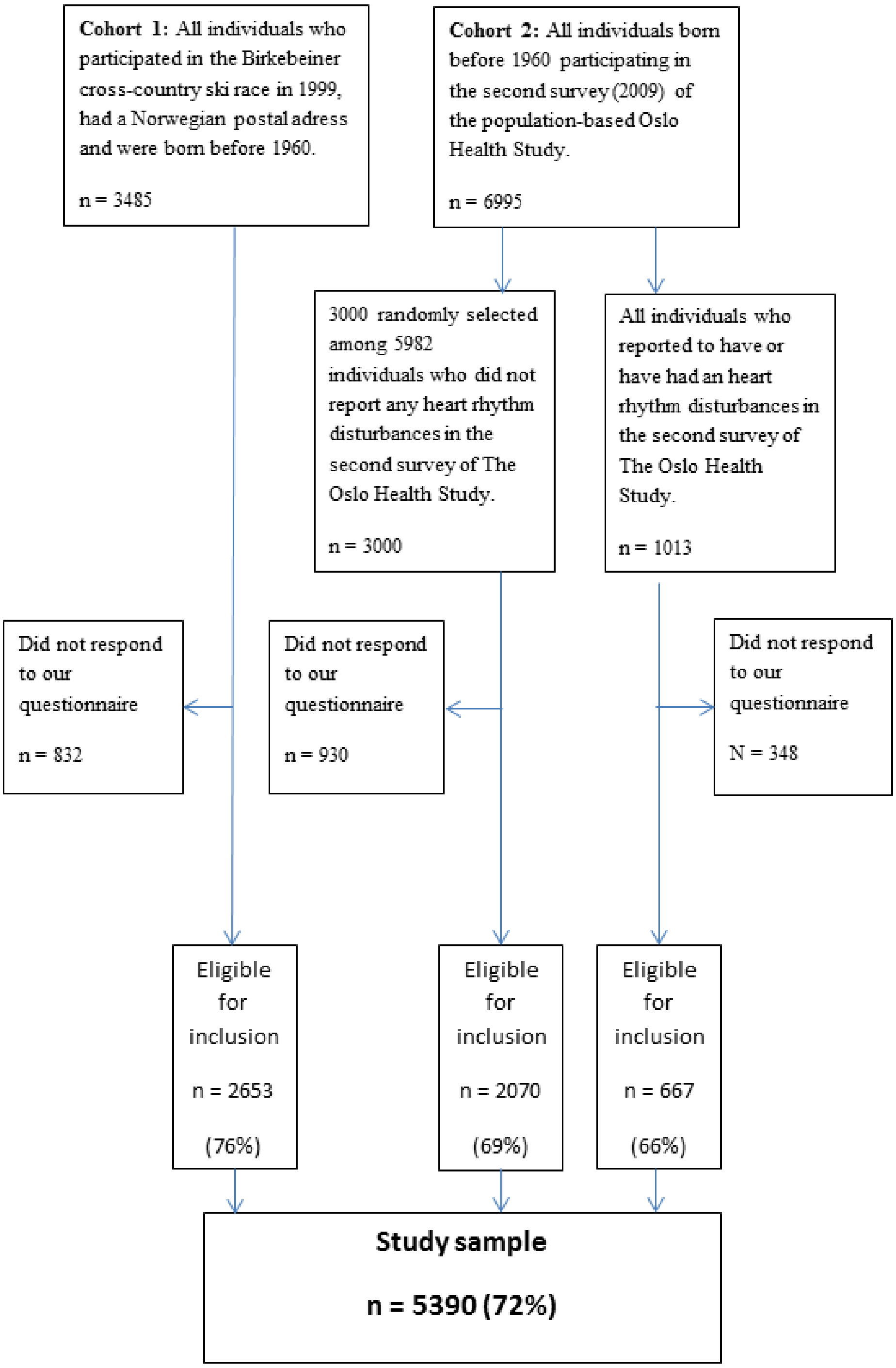
3.3.1 The cohort of veteran cross-country skiers

Based on result lists provided by the race organizer, all men and women who had participated in the Birkebeiner race in 1999, were aged ≥40 years at that time and had a Norwegian postal address were invited to take part in this study. Among 3485 invited skiers, 2653 (76%) responded. Among 3114 invited male skiers, 2366 (76%) men participated in the study. In total, 286 out of 371 (77%) invited female skiers took part in the study. In order to cover the range of exposure from physical inactivity to prolonged regular endurance exercise, the cohort of veteran skiers was combined with a subset from The Oslo Health Study.

3.3.2 The Oslo Health Study cohort

The Oslo Health Study was an age-stratified population-based health study [121]. Men and women aged ≥53 years (born in 1924, 1925, 1940, 1941, 1954 and 1955) who participated in the second survey of the Oslo Health Study in 2009 and had given consent to be re-contacted for further studies were invited to take part in the Birkebeiner Atrial Fibrillation Study. Out of 5982 individuals who had not reported heart rhythm disturbances in the 2009 survey, 3000 were randomly selected and invited to take part in the study. In addition, all 1013 individuals who had reported heart rhythm disturbances were invited, in order to maximize the number of endpoints. In total 2737 out of 4013 invited men and women from the Oslo Health Study (68%) participated in the Birkebeiner Atrial Fibrillation Study. In total, 1179 out of 1885 invited men (71%) and 1393 out of 2130 invited women (65%) responded.

Figure 2. Recruitment of participants to the Birkebeiner Atrial Fibrillation Study, based upon two distinct cohorts.



4 Methods

The data used in the Birkebeiner Ageing Study are entirely based on information obtained by questionnaires. When designing the questionnaire to this study, we chose questions that had been used in the Tromsø Study, in order to allow comparing analyses.

The data in the Birkebeiner Atrial Fibrillation Study were mainly obtained by questionnaires, but in 416 individuals with self-reported AF, hospital medical records were reviewed in order to confirm the AF diagnoses. English translations of the questionnaires are included in the appendix of this thesis.

4.1 Assessment of the main outcome atrial fibrillation

The main outcome of the papers I, II and III was AF. AF was measured differently in the three papers: In the papers I and III, AF was self-reported by questionnaires. In paper II, AF and AFL confirmed by ECG in the review of medical records were the main outcomes, while AF that was self-reported by questionnaires was a secondary outcome. Lone AF was another secondary endpoint of paper II.

4.1.1 Self-reported atrial fibrillation

In the Birkebeiner Ageing Study, AF was defined as positive response to the question *Do you have or have you had atrial fibrillation?*

In the questionnaire of the Birkebeiner Atrial Fibrillation Study, AF was assessed with two questions: *Do you believe yourself that you have or have had atrial fibrillation?* and *Have you been diagnosed as suffering from atrial fibrillation by a doctor?* In this study, we also included questions regarding the first AF diagnosis, subtype of AF and frequency of symptoms. AFL and other supraventricular tachycardia (SVT) were not assessed in the questionnaire but registered during the review of medical records.

4.1.2 Atrial fibrillation confirmed by ECG

When available, medical records were reviewed according to a predefined protocol for subjects who reported AF in the questionnaire of the Birkebeiner Atrial Fibrillation Study, stated a Norwegian public hospital as the place where AF had been diagnosed and gave consent. Among 694 study participants with self-reported AF, 574 (83%) gave consent to the review of their medical records. 92 participants reported that AF been diagnosed by their general practitioner (GP). Initially, we tried to identify and get access to these out-of-hospital medical records. However, this turned out to be a difficult task because the cases were distributed among very many GPs across Norway and because many of the GPs lacked routines for use of patient data in research. Some of the participants had been diagnosed abroad and some did not name the hospital where AF had been diagnosed, leaving 472 who had also named a hospital. In the end, records were available for review in 416 out of these 472 (88%) individuals.

The review of medical records in 18 different hospitals took place in the period between February 1st and June 1st 2013. Incident arrhythmias (AF, AFL, other SVT, atrioventricular block, ventricular tachycardia) up until 31.12.2012 were identified by ECGs. In cases of uncertain diagnoses, an endpoint committee consisting of two experienced cardiologists was consulted. In 19 cases where an ECG could not be found, diagnoses from the medical record text were used.

AF was classified as "lone" if the review did not reveal other relevant diseases (concomitant heart diseases, diabetes mellitus or surgery or treated infection during the past seven days before AF diagnosis). In individuals with hypertension (n=60), the arrhythmia was classified as without comorbid conditions only if echocardiography findings were available and normal.

4.2 Assessment of other outcomes

The endpoints of paper IV were leisure-time PA during the past year, current engagement in regular endurance exercise, palpitations, functional capacity, drug use and subjective health.

4.2.1 Leisure-time physical activity and endurance exercise

We assessed leisure-time PA during the past year using the question *State the movement and PA you engage in during your leisure time. If your activity level varies between summer and winter, note an average value. Tick the most appropriate box only*. A five-level scale was condensed into the four categories [3]: 1) Sedentary (reading, sitting still, other sedentary activity or light activities like walking, less than 4 hours per week); 2) Light PA (walking, cycling or other activity for at least 4 hours per week); 3) Moderate PA (recreational exercise, heavy gardening, for at least 4 hours per week); and 4) High PA (Regular hard exercise or competitive sports several times per week).

We specifically defined endurance exercise in the questionnaire as regular endurance exercise for at least 30 minutes at least 3 times per week with the purpose of increasing physical endurance capacity. The endpoint regular endurance exercise in paper IV was based on positive response to the question *Do you still engage in regular endurance exercise?*

4.2.2 Symptoms, drug use and subjective health

Palpitations during the past year were assessed with the question *Have you noticed sudden changes in your heart rate or heart rhythm in the past year?*

We used the NYHA functional classification (class I-IV) in order to assess functional capacity [122], and asked the participants to report how their heart disease impacts on their functional capacity (*If you have a heart disease, how does it impact on your ability to function?*) with four answer categories: I) No limitations. Ordinary PA does not cause undue fatigue, dyspnea or chest pain, II) Slight limitations of PA, but comfortable at rest. Ordinary PA results in fatigue, dyspnea or chest pain, III) Marked limitations of PA, but comfortable at rest. Even light PA causes fatigue, dyspnea or chest pain, and IV) Inability to carry out any PA without discomfort. Fatigue or chest pain may be present even at rest.

Drug use related to AF was assessed with the question *Do you use the following medicines as a result of atrial fibrillation?* with the following possible answers*:* Beta-blockers (e.g. Selo-Zok, Metoprolol, Sotalol, Sotacor, Emconcor), calcium-blockers (e.g. Isoptin, Verapamil, Veracard), amiodarone (Cordarone), flecainid (Tambocor), Digitoxin, digoxin (Lanoxin), acetylsalicylic acid (Albyl-E, Magnyl-E), dronedarone (Multaq), warfarin (Marevan) and dabigatran (Pradaxa).

Finally, we assessed subjective health with the question *How do you rate your own health?* with four answer categories (Poor, fair, good and very good) [123].

4.3 Assessment of the main exposure endurance exercise

Under the assumption that participation in a long-distance cross-country ski race when aged ≥65 years requires regular endurance exercise, *endurance sport practice* in the Birkebeiner Ageing Study was defined as belonging to the cohort of veteran cross-country skiers.

In the Birkebeiner Atrial Fibrillation Study, endurance exercise was specifically defined in the questionnaire as regular endurance exercise for ≥30 minutes at least three times per week with the purpose of increasing physical endurance capacity. The first question regarding endurance exercise used in the questionnaire, was *Have you ever been practicing regular endurance exercise?* (yes/no). Thereafter, the participants were asked to report the cumulative number of years they had been exercising regularly on an eight-level scale: Never, <5, 5-9, 10-19, 20-29,30-39, 40-49, 50-59, ≥60. In paper II, the scale was condensed from eight into five categories with cut-off at 40 years of exercise. In paper III, the scale was condensed into only four categories due to the lower number of women exposed to exercise in the study. Participants who had not answered any of these two questions were assumed not to have been exercising regularly and given the value Never.

4.4 Covariates

All covariates were self-reported by questionnaires. Diseases were assessed with the question *Do you have or have you had (name of the disease)?* In addition to age, gender, height and weight, we assessed the following established AF risk factors in the questionnaires of both the Birkebeiner Ageing Study and the Birkebeiner Atrial Fibrillation Study: Concomitant heart diseases (myocardial infarction, angina pectoris, heart valve pathology and heart surgery), hypertension, diabetes mellitus and hyperthyroidism. We also assessed the following less established risk factors and other possible confounding factors in both studies: Lipid-lowering treatment, stroke, use of tobacco and alcohol, education and marital status. We calculated BMI based on self-reported height and weight. In paper IV, we estimated CHA_2DS_2-VASc score using age, sex and self-reported CHD, hypertension, stroke and diabetes mellitus [82].

We used direct acyclic graphs (DAGs) to identify covariates appropriate for adjustment in all regression analyses. DAGs are causal graphs that summarize all relevant causal relations between an exposure and an outcome, and is a tool in the analysis of causal associations [124]. Causal graphs do not prove causality, but are based upon causal thinking and define a main exposure and a main outcome. In DAGs, covariates are defined as confounders, mediators or colliders. In the regression analyses, adjustments are made for confounders, but not for colliders. Mediators are adjusted for when aiming to estimate the direct effect between exposure and outcome.

4.5 Statistical analyses

Although having observed a higher AF prevalence in the Birkebeiner Ageing Study, we assumed a prevalence of around 5% in the power calculation of the Birkebeiner Atrial Fibrillation Study, due to a lower expected mean age of this study population. In order to find an OR of 1.5 with a 95% CI with a power of 80%, in a study where 50% were exposed to exercise and the prevalence of AF was 5%, around 5000 subjects were required.

We used Student's t-test for means of continuous variables and Pearson's Chi square of independence for categorical variables to compare characteristics of the study participants. In paper I, a linear regression analysis was used to calculate crude (cRDs) and aRDs with CIs and a logistic regression analysis was used to calculate the aOR with CI. In paper II, III and IV, aORs with CIs were calculated by weighted logistic regression analyses. We tested all relevant covariates, but included only established risk factors and covariates changing the estimates with ≥10% in the final models.

In paper II and III, we adjusted for different selection probabilities by using inverse probability weighting: Study participants who were invited because they had previously participated in the Birkebeiner race or because they had previously reported arrhythmias in The Oslo Health Study were weighted by one (all eligible individuals were invited). Participants who were randomly selected among participants in the Oslo Health Study were weighted by two (3000 out of 5982 were invited). Due to the different selection probability, we report the weighted prevalence for the participants in the Oslo Health Study in paper II, and weighting was used in all regression analyses of paper II and III.

In the papers II and III, we excluded study participants who had been invited because they had reported hearth rhythm disturbances in the Oslo Health Study but turned out not to have any arrhythmias. In paper III, we excluded women aged >75 years in order to reduce recall bias. In order to increase the comparability between the AF subpopulations of the study, we excluded individuals aged >85 years in paper IV. Due to the strong positive relation between age and risk of AF, we performed sensitivity analyses after exclusion of men aged >75 years to explore the influence of age distribution on the risk estimates in paper II. In addition, sensitivity analyses after exclusion of men diagnosed with arrhythmia before the age of 40, men invited because they had previously reported heart rhythm disturbances and men with self-reported AF but unavailable medical records were conducted. In paper II we reported estimates for the two distinct cohorts (Birkebeiner skiers and participants from the Oslo Health Study) separately and for the whole study sample.

All statistical analyses were conducted using SPSS version 20.0 (IBM, Armonk, New York, USA) or STATA version 12.1 (StataCorp LP, Lakeway Drive, Texas, USA).

4.6 Ethical considerations

The studies in this thesis were approved by the Regional Committee for Medical and Health Research Ethics (REK) and comply with the Declaration of Helsinki. Together with the questionnaires, all invitees received invitation letters that had been approved by REK. Informed written consents to participate in the study were obtained. The review of medical records was only performed for participants who had actively given a written informed consent to the review. Approvals for the review of medical records were obtained from the responsible authorities for research and data protection for each hospital reported by at least one participant. Inclusion in the studies was considered not to have any harmful effects for the participants.

5 Results

5.1 Paper I: Endurance sport practice as a risk factor for atrial fibrillation

Title: Increased risk of atrial fibrillation among elderly Norwegian men with a history of long-term endurance sport practice

Compared to men of the same age from the general population of Tromsø, veteran cross-country skiers aged ≥65 years (mean age 69, range 65-90 years) had a low prevalence of the established AF risk factors CHD, hypertension and diabetes mellitus. The crude prevalence of AF was 13.2% in the veteran athletes and 11.6% in the general population. The prevalence of AF after exclusion of persons with CHD was 13.0% in the veteran athletes and 9.8% in the general population. After multivariable adjustment for age, height, BMI, CHD, hypertension, diabetes mellitus, smoking, alcohol consumption, leisure-time PA during the past year and education, endurance sport practice gave an added risk of AF of six pp (aRD 6.0 (CI 0.8-11.1)), corresponding to an aOR of 1.90 (CI 1.14-3.18). The risk of AF increased with 0.4 pp per added year of age and with 0.3 and 0.6 pp per cm of height and unit of BMI added, respectively. Also hypertension and CHD were significantly associated with an added risk for AF.

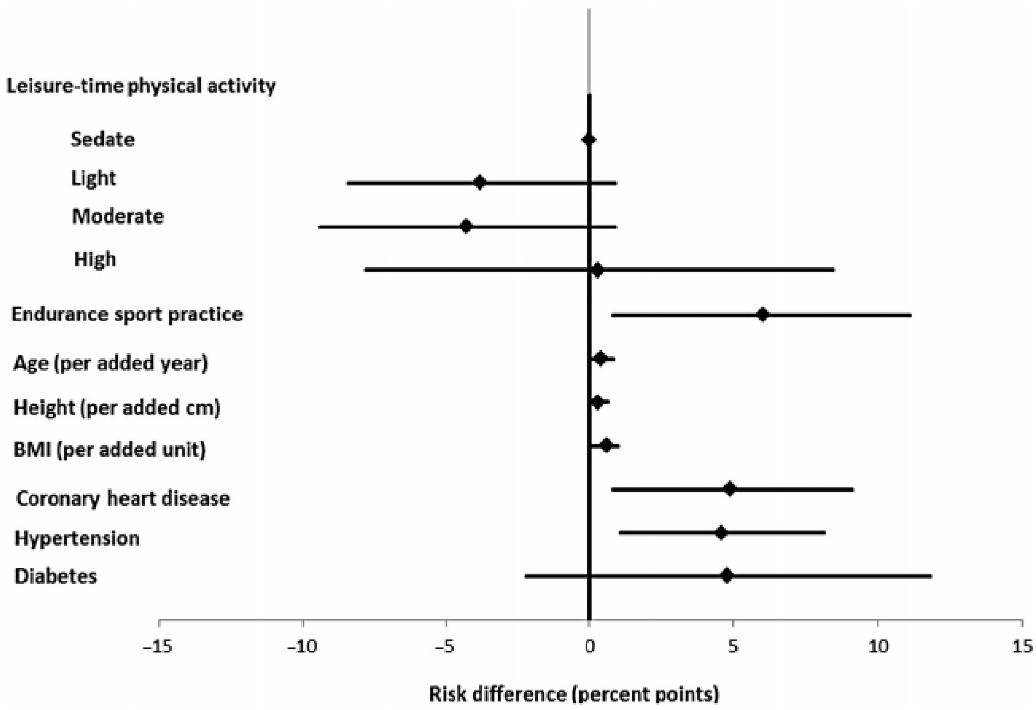


Fig. 2. Studied risk factors for atrial fibrillation. Estimated atrial fibrillation risk differences with 95% confidence intervals by selected covariates. Both study populations analyzed together, men 65–90 years old.

5.2 Paper II: Years of regular endurance exercise was associated with a graded increased risk of atrial arrhythmias in men

Title: Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter

The prevalence of self-reported AF was 12.5% among the veteran cross-country skiers (mean age 66, range 53-92 years) and the weighted prevalence among the participants in the Oslo Health Study was 10.3%. While AF was confirmed by ECG in 219 out of 306 men (72%) with self-reported AF and available medical records, 52 (17%) had AFL. After multivariable adjustment for age, height, concomitant heart disease, hypertension, diabetes mellitus and cohort affiliation, cumulative years of regular endurance exercise were associated with a gradually increased risk of AF with an aOR for AF of 1.16 (CI 1.06-1.28) per ten years of exercise, 1.16 (CI 1.00-1.36) among the skiers and 1.20 (CI 1.06-1.35) among the men from the Oslo Health Study. Regular endurance exercise was also associated with a gradually increased risk of AFL. The aOR for AFL per ten years of exercise was 1.42 (CI 1.20 – 1.69) and did not differ between the two cohorts. The aORs per ten years of exercise were 1.26 (CI 1.10 to 1.44) for lone AF and 1.12 (CI 1.04-1.19) for self-reported AF.

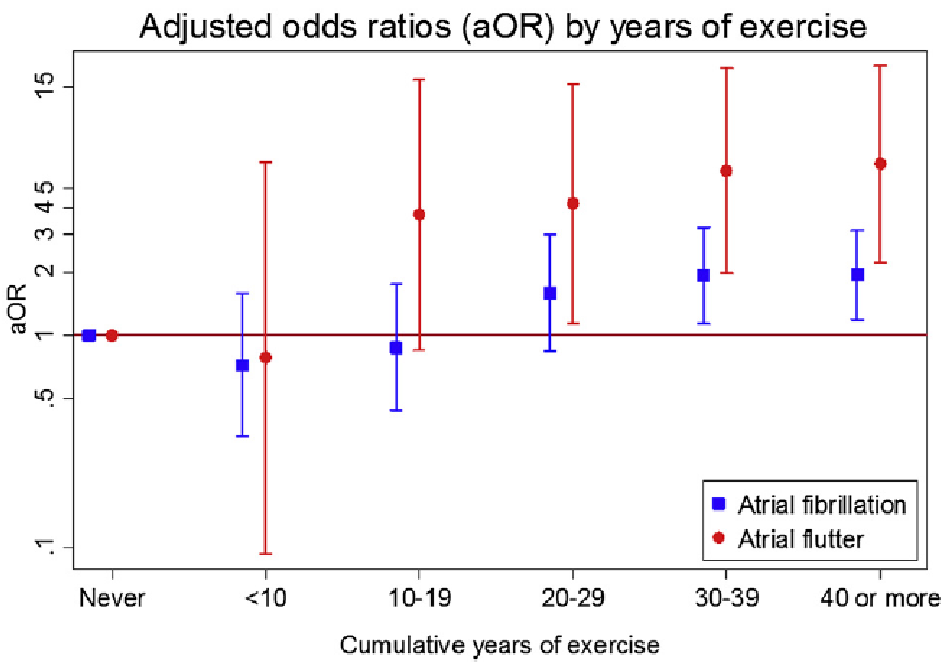


Figure 2. Adjusted odds ratios with 95% CIs for AF (n = 219) and atrial flutter (n = 52) by categories of exercise years, men aged 53 to 92 years (n = 3,545). Adjusted for age, height, heart disease, hypertension, diabetes mellitus, high-intensity exercise during the previous 12 months, and cohort affiliation.

5.3 Paper III: Prolonged endurance exercise might be associated with atrial fibrillation in women

Title: Does endurance exercise cause atrial fibrillation in women?

In total, 110 out of 1449 women reported AF. The prevalence of self-reported AF among female veteran cross-country skiers (n=278) was 8%. While 815 women had never exercised regularly, 634 had exercised regularly at some point of life, 89 of them for ≥40 years. Women who had never exercised regularly were older compared to women who had exercised at some point of life. Women who had exercised ≥20 years had a lower mean BMI and less hypertension and lipid-lowering treatment than women who had exercised <20 years. After multivariable adjustment for age, BMI, concomitant heart disease, hypertension, diabetes mellitus and cohort affiliation, women who had exercised for ≥40 years seemed to have an increased risk of AF of borderline significance (aOR 2.18 (CI 0.94-5.06)) compared to women who had never exercised regularly.

5.4 Paper IV: The majority of veteran athletes still engaged in regular physical activity and exercise after the onset of atrial fibrillation

Title: Physical activity, symptoms, medication and subjective health among veteran endurance athletes with atrial fibrillation

AF was reported by 322, medical records were available for review for 177 and AF was confirmed in 140 veteran cross-country skiers. Among the study participants from the general population, AF was confirmed in 118 cases. Among veteran skiers, 52% had paroxysmal AF, 23% had persistent AF and 24% had permanent AF, while the corresponding proportions in the general population were 52%, 17% and 30%. Veteran athletes with confirmed AF were older and had a higher prevalence of co-morbid conditions than veteran athletes without AF, but were younger and had a lower BMI and less co-morbidity than their counterparts with AF in the general population. Only 11% of the veteran skiers with AF were inactive, 70% reported moderate or high PA during the past year and 64% still engaged in regular endurance exercise. After multivariable adjustment for age, sex, BMI, co-morbid conditions and number of completed Birkebeiner races, AF was associated with poor subjective health among veteran athletes (aOR 2.8 (CI 1.7-4.6)). Almost two out of three reported palpitations during the past year and one out of three had experienced reduced functional capacity, but symptoms did not differ significantly between the veteran athletes with AF and the general AF population, between AF subtypes or between AF with and without co-morbid conditions. One out of three with AF and an estimated CHA_2DS_2-VASc score ≥2 was not treated with OAC.

6 Discussion

The results of this thesis support that endurance sport practice might be a risk factor for AF in men aged ≥65 years, suggest a graded positive association between years of regular endurance exercise and risk of atrial arrhythmias in men, and indicate that prolonged endurance exercise might be associated with an increased risk of AF also in women. In addition, it has been demonstrated that the majority of veteran athletes remains physically active and engage in regular endurance exercise even after the onset of AF. The study populations, including veteran athletes that on average have been exposed to regular endurance exercise and sport practice for very many years, confirmation of AF diagnoses during a review of medical records, very high attendance rates and the collection of a broad specter of possible confounding factors, are main strengths of these studies. Some important issues related to the study design, exposure and outcome measurements and confounding, however, will be discussed.

6.1 Methodological considerations

The observational design of the studies of this thesis has some important limitations. Observational studies can be hampered by selection bias, information bias and confounding. Furthermore, the design does not allow any conclusions about a causal relationship.

6.1.1 Study design

To conduct a randomized controlled trial in order to investigate the relation between prolonged endurance exercise and risk of AF, might seem unfeasible and would also have carried some ethical problems. Study participants would have to be followed prospectively for a long time, with high risk of drop-outs and problems with competing risk. Therefore, a retrospective study design appeared to be the most feasible in order to study this association. As it might be assumed that participation in the Birkebeiner race requires regular endurance exercise, the use of participation lists from the race organizer provides some objective information on the exposure, in addition to the retrospective self-reporting of exercise.

In paper I, we used cross-sectional data from the Birkebeiner Ageing Study and the Tromsø Study. The main exposure was participation in the Birkebeiner race and the main outcome was self-reported AF. This study design might be affected by selection bias, because the participation of the study might be associated with both the exposure and the endpoint: Individuals who had discontinued their endurance sport practice due to AF (or other diseases) did not have the opportunity to participate in the study. This "healthy exerciser effect" might have caused an underestimation of the AF prevalence among the veteran skiers and the AF risk estimates.

Also in the Birkebeiner Atrial Fibrillation Study, we used cross-sectional data. In this study, however, the study population was based upon a cohort of veteran skiers that had been participating in the Birkebeiner race many years earlier (1999) and the study might be characterized as a retrospective cohort study [125]. Because AF is uncommon before the age of 40 and all skiers who were aged ≥40 in 1999 were invited, the results of this study are less likely to be affected by a "healthy exerciser effect". On the other hand, individuals with AF who had been exposed to endurance exercise might have been more prone to participate in the study, and this possible selection bias might have caused an overestimation of the risk estimates. However, as high attendance indicates that the study population gives satisfactory information about the target population [126], an overrepresentation of AF cases is less likely. Even in studies with much lower attendance rates, it has been demonstrated that effect estimates are not necessarily biased by under- or overrepresentation of the exposure [127, 128].

While inadequate control groups and the lack of a reference point in the general population have been pointed out as a weakness of previous studies [108, 129], in the Birkebeiner Atrial Fibrillation Study we combined two distinct cohorts with the aim to cover the whole range of exposure from physical inactivity to prolonged endurance exercise. The combination of two cohorts that differ in many aspects might be questioned, because the cohorts might differ in unmeasured characteristic that could influence the risk of AF, like psychosocial factors and a family history of cardiovascular diseases [130, 131]. However, the association between years of exercise and risk of AF was consistent also when the two cohorts were analyzed separately (paper II).

The low number of female participants confines the possible gender perspectives of the Birkebeiner study populations. Female response rates were at the same level as in men, but the low proportions of women participating reflect that women represent a minority among non-elite athletes in long-distance cross-country ski races.

6.1.2 Atrial fibrillation measurements

AF studies are limited by the natural course of the disease. Firstly, 30-40% of the individuals with AF might be asymptomatic [132-134]. Secondly, in individuals with paroxysmal AF, the arrhythmia can only be diagnosed with certainty during an attack. Thus, AF studies are likely to have high rates of AF cases that are falsely classified as without arrhythmia (low sensitivity). The proportion of persons with undiagnosed AF might be especially high in our study populations, as old people often have less symptomatic AF than younger [134-136].

As demonstrated in figure 1, the prevalence of AF was higher in Tromsø 6, where AF was self-reported, compared to other prevalence studies. Increased sensitivity might be an advantage of self-reporting of AF, as also undiagnosed cases are counted. A weakness of our studies is that false negative rates were not investigated. Thus, we were unable to conclude regarding the overall validity of the AF measures used in our studies.

In the review of medical records in the Birkebeiner Atrial Fibrillation Study, we were able to assess the specificity of the AF questions used in the study, and table 3 shows confirmed arrhythmias according to the two questions used in the questionnaire. Among participants with self-reported AF, the diagnosis was confirmed in three out of four, while around 16% had other arrhythmias. In 11% the review did not reveal any arrhythmia. In comparison, in the Physician's Health Study, 7% of those with self-reported AF did not have a confirmed AF diagnosis [137].

Table 3: Proportions with arrhythmias confirmed in the review of medical records among individuals with self-reported atrial fibrillation according to the two different question used in the Birkebeiner Atrial Fibrillation Study (n=416).

	n [a]	Results of the review, numbers and proportions (%)				
		No arrhythmia	Atrial fibrillation	Atrial flutter	Other SVT [b]	Other arrhythmias
Do you believe yourself that you have or have had atrial fibrillation?	351	40	255	28	21	7
		11.4	72.6	8.0	6.0	2.0
Have you been diagnosed as suffering from atrial fibrillation by a doctor?	365	39	270	29	20	7
		10.7	74.0	7.9	5.5	2.0

[a] Number of review medical records among study participants who answered this question positively, gave consent to the review and named a Norwegian hospital where atrial fibrillation had been diagnosed.
[b] Supraventricular tachycardia

A key question is whether the misclassification is differential and associated with the exposure. While physically inactive individuals might be less likely to experience AF symptoms [134], more active individuals might recognize symptoms earlier or be more prone to misinterpret harmless palpitations as AF. This might have caused an overestimation of the AF risk estimates. On the other hand, athletes more often have typical vagal AF with lower heart rates and paroxysms during night [115, 138], and might be more prone to ignore symptoms. Athletes also more often have paroxysmal AF that might be more challenging to diagnose [115], and this might have caused an underestimation of the AF risk estimates in the Birkebeiner Atrial Fibrillation Study.

While most previous studies have not differentiated between AF and AFL [8, 9, 139], the differentiation between these two atrial arrhythmias is an asset of our study. Subjective distinguishing between AF and AFL can be difficult and AFL was not assessed in the questionnaire. Individuals who knew that they had been diagnosed with AFL and not AF might have answered "no" on the questions regarding AF, leading to an underestimation of the AFL risk estimates.

Medical records were available for 60% of the individuals with self-reported AF. The proportion with available records among those with self-reported AF did not differ between skiers and non-skiers, but were slightly higher in individuals who reported ≥30 years of regular exercise compared to the other groups of exposure. Table 4 shows confirmed arrhythmias by the two AF questions and cohort. The proportion of false positives was highest among the non-skiers (13.0% versus 9.6%) for the question *Do you believe yourself that you have or have had atrial fibrillation?* that was used in paper II, which might have caused an underestimation of the AF risk estimates in our study. On the other hand, there were less false positives among those who had been exercising <10 years compared to those who had exercised ≥10 years (data not shown), which might have caused an overestimation of risk estimates. There were no differences within those who had exercised ≥10 years (data not shown). Thus, the gradient demonstrated with increasing years of regular exercise is not likely be explained by differences in the self-reporting.

Table 4: Proportions with atrial arrhythmias confirmed during the review of medical records among individuals with self-reported atrial fibrillation according to the two different question used in the Birkebeiner Atrial Fibrillation Study (n=416).

	Results of the review, numbers and proportions (%)					
	General population			Skiers		
	No arrhythmia	Atrial fibrillation	Atrial flutter/ SVT[b]	No arrhythmia	Atrial fibrillation	Atrial flutter/ SVT[b]
Do you believe yourself that you have or have had atrial fibrillation? (General population n = 185, skiers n = 166[a])	13.0	76.2	8.6	9.6	68.7	19.8
Have you been diagnosed as suffering from atrial fibrillation by a doctor? (General population n = 191, skiers n = 174[a])	10.5	79.1	8.4	10.9	68.4	18.9

[a] Number of review medical records among study participants who answered this question positively, gave consent to the review and named a Norwegian hospital where atrial fibrillation had been diagnosed.
[b] Supraventricular tachycardia

While some previous studies have used hospitalization recorded with ICD-10-codes in national in-patient registers [140, 141], others have used self-reported AF and obtained medical records for confirmation of the diagnosis [103, 142]. In order to isolate lone AF, prescription of flecainid and sotalol recorded from the Norwegian prescription registry was used as a surrogate measure for lone AF in one study [143]. All measures have limitations and comparison of results between studies is difficult. Even in studies where AF has been diagnosed using the gold standard ECG [100, 105, 106], false negative rates have not been assessed and the overall validity is therefore unknown. The results of the Birkebeiner Atrial Fibrillation Study are strengthened by the consistency between the various AF measures used in the study.

6.1.3 Measurements of other endpoints

A limitation of our studies is that we did not assess other symptoms than palpitations and functional capacity. Palpitations are, however, the most commonly reported among AF-related symptoms [70], and might be more specific than for example dyspnea. The NYHA-classification measures the physical functional capacity and was originally developed for use in heart failure patients, but has also been validated in AF patients [70, 122]. It assesses functional capacity related to fatigue, shortness of breath or chest pain, and therefore gives some information also about these AF-related symptoms.

Self-reports of OAC use might provide imprecise information on adherence [85]. Furthermore, the Birkebeiner Atrial Fibrillation Study do not provide information on the use of novel OACs because these were not in routinely use in Norway at the time of the study [144].

Self-rated health is a reliable and valid measure of subjective overall health status, including biological, psychological and social dimensions of health, and is associated with morbidity and mortality [123, 145, 146]. It has also been used previously in studies of AF patients [71].

6.1.4 Measurement of endurance exercise

In paper II and III, we aimed to investigate a dose-response relationship in the association between endurance exercise and risk of AF and designed our own questions and scales in order to assess prolonged endurance exercise. We used an eight-level scale with a cut-off at 60 years of exercise. Thus, at least partly, the exposure occurred many decades ago and might have been difficult to recall accurately. Furthermore, the results might have been affected with recall bias: Participants with AF might have been more prone to over-report previous exercise than individuals without AF, causing a differential misclassification that could have influenced the effect estimates positively.

6.1.5 Measurement of co-morbid conditions and confounding

Confounders are variables that are associated both with the exposure and the outcome [125]. While the results of previous studies investigating the risk of AF by endurance sport practice have been questioned because many of the participants have been exposed to possible confounding factors [99, 100], the prevalence smoking and co-morbid conditions was relatively low in our studies. Furthermore, the assessment of a broad specter of AF risk factors, co-morbid conditions and other possible confounding factors is an asset of both the Birkebeiner Ageing Study and the Birkebeiner Atrial Fibrillation Study. Although self-reporting might be affected by recall bias, previous studies suggest an acceptable validity of self-reported data on diseases like CHD, hypertension [147], diabetes mellitus and stroke [148], and smoking [149].

In paper IV, we estimated CHA_2DS_2-VASc scores based on age, sex and self-reported CHD, hypertension, stroke and diabetes mellitus [82]. Congestive heart failure and vascular diseases others than CHD were not assessed in our questionnaire. This method provides only rough estimates for stroke risk, but was useful in order to assess the use of OAC in AF patients with concomitant stroke risk factors.

6.2 Discussion of the main results

6.2.1 Endurance sport practice as a risk factor for atrial fibrillation

In the Birkebeiner Ageing Study (paper I), we demonstrated a high prevalence of AF of 13.2% among male veteran cross-country skiers. This is in concordance with a previous study of veteran Birkebeiner skiers, where the prevalence of AF was 16.7%. [94]. A higher prevalence of concomitant cardiovascular risk factors and diseases in the previous study might, at least partly explain the difference between the studies [96].

Endurance sport practice, defined as participation in the Birkebeiner race, seemed to be a risk factor for AF among men aged ≥65 years. This result is in line with those from previous studies conducted in younger male elite orientation runners, former professional cyclists and non-elite marathon runners [8, 9, 100]. The aRD estimated in the Birkebeiner Ageing Study corresponds to an aOR for AF of 1.90 (CI 1.14-3.18). This is close to the risk estimate (pooled RR for AF 1.98 (CI 1.00-3.94)) reported in a recent meta-analysis that included almost 2,000 endurance athletes [150].

In a previous study conducted among men and women aged ≥65 years in the United States, leisure-time PA seemed to reduce the incidence of AF in a graded manner [109]. The most active group in this study, however, had an average activity level corresponding to 1840 kcal/week, which is likely to be far below that of the majority of Birkebeiner skiers. Our results are also in contrast with the Physician's Health Study, where no association between endurance exercise and risk of AF was found among male physicians aged >50 years. The authors of this paper suggest an underestimation of the AF risk due to a "healthy exerciser effect", or that older individuals exercise less vigorously than younger [103]. The stronger exposure to exercise in our studies increases their power to detect an association between exercise and AF and is likely to explain the controversial results between ours and these previous studies.

In a recently published study of cyclists in New Zeeland, no association was found between participation in a bicycle race and hospital admissions due to AF when compared to the general population [151]. In this study, the majority of participants were aged <50 years, only 66 cases of AF were registered and the study might therefore not have had enough power to detect an association. In an analysis derived from two large prospective studies of walkers and runners, cardiac arrhythmias were not related to walking or running intensity or to marathon participation or performance [152]. This study, however, did not differentiate between arrhythmias.

6.2.2 Prolonged endurance exercise and risk of atrial fibrillation

In the Birkebeiner Atrial Fibrillation Study (paper II), we demonstrated a gradually increased risk of AF by cumulative years of regular endurance exercise in men. This result is supported by the results of a study by Andersen, et al, conducted among Swedish participants in the 90-kilometer cross-country ski race Vasaloppet. In this study, number of completed races was associated with an increased risk of AF in a graded manner. Men who had completed ≥three races had a significant higher risk of AF, with an adjusted hazard ratio (HR) of 1.27 (CI 1.02–1.57) compared with participants who had only completed one race [140]. A main limitation of this study was the lack of a reference point in the general population [129].

Also a population-based cohort study published in 2014 supports a dose-response relationship between exercise and the risk of AF. More than 44,000 Swedish men aged 45-79 were included in this study, where weekly hours of exercise at age 30 were associated with an increased risk of AF later in life. Similar to in our study, the risk of AF seemed to increase gradually, but was not statistically significant until the highest level of exercise (>5 hours exercise/week) [141]. The main strength of this study is that it was conducted in a large cohort representing the general Swedish male population with a high number of endpoints.

Elousa, *et al,* have suggested a threshold of 1500 lifetime hours of exercise for the development of AF [105]. However, as elite athletes in endurance sports might exercise up to 1000 hours a year, and many non-elite athletes exercise 300-500 hours [153], a very high prevalence of AF should be expected with this estimated threshold. In contrast, Bjørnstad, *et al,* found no cases of AF in a follow-up study of Norwegian former elite athletes [98]. The result of paper II supports a gradually increased risk by amount of exercise rather than a threshold beyond where AF risk is increased. The AF risk was not statistically significantly increased until ≥30 years of exercise, but this might be due to lack of power of the study. Furthermore, in the light of individually different risk profiles, to set an absolute threshold seems unreliable.

Few previous studies have differentiated between AF and AFL [113]. In our study, 13% of the male veteran athletes with confirmed AF also had AFL. Among the Finnish orientation runners studied by Karjalainen, *et al*, 25% had AFL in addition to AF [8]. In a study of Italian former professional cyclists, AFL was more common than AF [9]. The result of a retrospective case-control study including 61 Belgian patients with lone AFL suggested that a history of endurance sport practice may be a risk factor for AFL [154]. While these previous studies have not estimated the risk of AFL by endurance exercise, cumulative years of regular endurance exercise was associated with a graded increased risk of both AF and AFL in the Birkebeiner Atrial Fibrillation Study. This result suggests that the dose of endurance exercise might play a role in the pathophysiology of both arrhythmias.

Despite a few negative studies and scepticism among some authors [99, 150, 155], others conclude that there is enough evidence to suggest a causal association between endurance sport practice and an increased risk of AF [113, 156-159]. However, many questions remain unanswered regarding the duration, amount, intensity and type of exercise that might increase the risk of AF [157].

6.2.3 Prolonged endurance exercise and risk of atrial fibrillation in women

Furthermore, the lack of data pertaining to women is a limitation of all previous studies [7, 115, 129]. In the Birkebeiner Atrial Fibrillation Study we investigated the association between endurance exercise and risk of AF in both genders. Although limited by weak power, the result of paper III indicates that prolonged endurance exercise might be related to an increased risk of AF also in women.

The lack of an association between endurance exercise and sport practice and risk of AF in women in previous studies might either have epidemiological explanations or be due to real gender differences. As demonstrated in figure 1, women experience AF five to ten years later than men, and low numbers of AF cases in previous studies might at least partly explain why no association has been demonstrated between exercise and AF in women. This is illustrated by the study of participants in Vasaloppet, where only 12 cases of AF occurred during >50,000 person-years of follow-up among women [140]. The INTERHEART-study showed that also CHD occurs later in women than in men [67]. In the Birkebeiner Atrial Fibrillation Study, women were younger and had lower prevalence of CHD, hypertension and diabetes than men, and lower prevalence of established AF risk factors is likely to be part of the explanation.

Also gender differences in the exposure to endurance sport practice might play a role. The low proportions of women among the veteran skiers in our studies (7.8% in the Birkebeiner Ageing Study and 10.6% in the Birkebeiner Atrial Fibrillation Study) demonstrate that women are less likely to participate in endurance sports events. This is supported by the results of a study conducted among Danish people who exercised regularly, where only 22% of the women compared to 37% of the men had participated in endurance sports competitions [160]. In the same study, 5% of the women compared to 10% of the men exercised >10 hours per week. In a study of Danish runners, 18% of the women compared to 34% of the men reported an average weekly running distance of >30 kilometres, while 2.5% and 10.1% reported a distance of >50 kilometres [161].

Finally, physiological gender differences might be part of the explanation. Women have physiological smaller hearts and higher heart rates, and low heart rates seem to predict

AF only in men [143, 162]. Atrial morphological and functional changes have been demonstrated in female athletes [163], but in a recent study, female veteran athletes had less pronounced remodeling, lower sympathetic tone and lower blood pressure than their male counterparts [164]. The interplay between endurance exercise, sex hormones release and electrophysiological gender differences remains an unexplored field.

6.2.4 Characteristics of atrial fibrillation in veteran athletes

Paroxysmal lone AF in middle-aged men exposed to prolonged endurance exercise has previously been characterized as the typical clinical profile of exercise-related AF [113]. In the Birkebeiner Atrial Fibrillation Study of male skiers with a mean age of 69 years, 24% had permanent AF and 43% had co-morbid conditions, indicating that veteran athletes with AF represent a more heterogeneous population.

The clinical presentation of AF might vary between AF subtypes and between men and women, and is influenced by age, co-morbidity and socioeconomic status [70]. Furthermore, the lack of standardized outcome parameters in many AF studies limits the possibility of comparison between studies [132]. Palpitations and reduced functional capacity were less frequent both in veteran skiers and in the general AF population in the Birkebeiner Atrial Fibrillation Study than in previous studies conducted in general AF populations [72, 165]. While 60% had symptoms that required termination of sport activity in a study of 30 Dutch athletic men with paroxysmal AF [139], the high proportion engaging in exercise also after the onset of AF in our study supports that many individuals with AF have relatively mild symptoms [134]. Still, AF was associated with poor subjective health among veteran skiers. While this association was robust also after adjustment for co-morbid conditions in a previous study [71], subjective health seemed to depend on co-morbidity in the Birkebeiner Atrial Fibrillation Study.

Both among the skiers and in the general population in the Birkebeiner Atrial Fibrillation Study, two out of three with AF and an estimated CHA_2DS_2-VASc score ≥2 used OAC. Although the CHA_2DS_2-VASc score is roughly estimated in this study and self-reporting might provide imprecise information on treatment adherence [85], the result might indicate a lower OAC use in our study populations compared to other general AF populations [166]. In general, veteran athletes might be less prone to any drug treatment [115], but there are no data to support not to treat veteran athletes with AF and a CHA_2DS_2-VASc score ≥2 with OAC in order to prevent stroke.

The proportion using rate-controlling drugs was lower in the veteran skiers with AF compared to the general AF population in our study. This might be due to lower heart rates in athletes, or because athletes refuse to use treatment that might reduce sports performance [115]. On the other hand, the proportion using rate-controlling drugs was higher than in a previous study conducted in France during the 1990's [167]. This might reflect differences in symptom burden, co-morbidity and general health status or in AF medication prescription between countries and over time.

6.2.5 Physical activity and endurance exercise in veteran athletes with atrial fibrillation

Almost 90% of the veteran athletes were physically active also after the onset of AF, and two out of three still engaged in regular endurance exercise. Importantly, this demonstrates that veteran athletes continue to profit from the benefits of PA and exercise also after the onset of AF. In a short term, regular exercise might reduce resting heart-rates and symptoms and improve heart rate variability, exercise capacity, the ability to carry out activities of daily living and health-related quality of life in persons with AF [168-170]. In the long term, also individuals with AF can profit from the universal benefits of regular PA and exercise in terms of reduced mortality and morbidity [40].

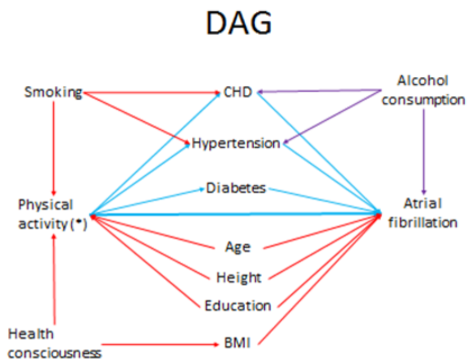
6.2.6 General discussion

The exposure to PA or exercise varies largely and might explain the controversial results between studies. While large prospective cohort studies have typically investigated the risk of AF by self-reported PA [109, 110, 142], case-control and cohort studies with smaller sample sizes have been conducted in different populations of athletes [8, 9, 100]. The term "athlete" refers to individuals engaging in regular sport practice, but there is a wide gap between recreational exercise and elite level competitive sports, and a clear-cut definition has not existed. Furthermore, physiological adaptions to endurance exercise might differ between individuals engaged in PA and athletes exposed to prolonged regular endurance exercise, and a threshold between physiological and pathological adaptions has not been established [7].

The results of paper I indicate that light or moderate PA during the past year might reduce the risk of AF, although not significant in our study. This supports the results of a Swedish study that demonstrated a reduced risk of AF by amount of PA among men with a mean age of 60 years [141], and those from the Cardiovascular Health Study (90), where self-reported PA was associated AF in a U-shaped manner in men and women aged ≥65 years. While moderate intensity was associated with lower incidence of AF (HR 0.72, CI 0.58-0.89), those who reported the highest activity level had the same AF incidence as the inactive individuals. Two studies have investigated the association between PA and risk of AF in women exclusively, and demonstrated that higher levels of PA were associated with a lower prevalence of AF [142, 171]. In contrast, two recent meta-analyses conclude that there is no association between leisure-time PA and risk of AF [150, 172], and a Norwegian study by Thelle, *et al*, suggest an increased risk of AF in absence of concomitant heart disease (lone AF) by self-reported leisure-time PA at age 40 [143].

While endurance exercise seems to increase the risk of AF, PA might reduce the risk through a preventive effect on AF risk factors like CHD, hypertension and diabetes mellitus (Figure 3). Therefore, the prevalence of risk factors others than exercise in the studied population will influence the estimated association between exercise and AF. In older populations, where these risk factors are likely to be more prevalent than in younger populations, a stronger AF risk reduction by PA might be expected. This might be important also after adjustment concomitant diseases, as cardiovascular conditions might be unrecognized in many studies.

Figure 3. Simplified direct acyclic graph (DAG) illustrating the association between physical activity and endurance exercise and atrial fibrillation.



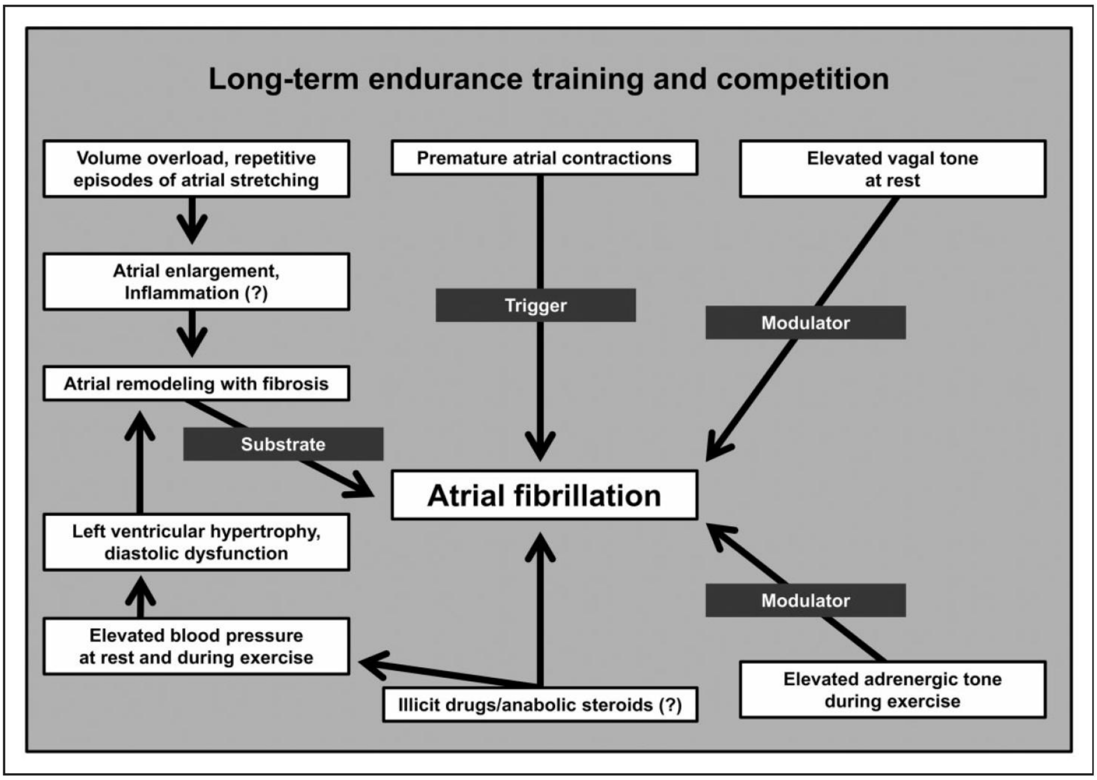
(*) Endurance sport practice is covered by the term physical activity. Due to different underlying mechanisms in the association with AF, self-reported leisure time PA was adjusted for when estimating risk differences for AF.

Arrows and covariates not influencing the analysis are excluded. The highlighted arrow illustrates the direct association between sport practice and atrial fibrillation. The other arrows illustrate intermediate covariates in the association (blue), confounding (red) and colliding (violet) covariates.

There is a strong positive association between age and risk of AF [66]. At the same time, older individuals are more likely to report a high number of years of cumulative years of exercise than younger. The prevalence of AF was higher than expected in the youngest and lower than expected in the oldest participants of the Birkebeiner Atrial Fibrillation Study, and the effect estimates increased slightly in the sensitivity analysis performed after exclusion of men aged >75 years. This supports that our results are not an effect of increasing age.

Endurance sports like cross-country skiing are highly dynamic sports characterized by a high cardiovascular demand during exercise and competition. During dynamic exercise there is an increase in heart rate, stroke volume, cardiac output and systolic blood pressure [4]. Mechanisms for AF in endurance-trained individuals are not fully understood, but myocardial remodeling and left atrial dilatation related to high volumes and pressures during exercise, atrial fibrosis caused by inflammation, increased vagal tonus and electrolyte disturbances during exercise are among the suggested mechanisms [113, 115, 156, 173]. A summary of factors that might influence the development of AF in athletes is shown in figure 4.

Figure 4. Synopsis of factors that might influence the development of atrial fibrillation in athletes, from Wilhelm [156].



Structural myocardial changes like dilatation or fibrosis could cause electrical dissociation between cardiac muscle bundles, and such local electro-anatomical substrates might facilitate re-entry circuits that can induce or maintain arrhythmias [64]. Studies have demonstrated an increase in myocardial biomarkers after endurance sport practice, suggesting an acute effect on the heart, possible caused by volume overload [156, 174]. Other studies have showed that left atrial dilatation is prevalent in many athletes and suggested that this might be a result of chronic exposure to high pressures and volumes [95, 100, 106, 175]. Among veteran Birkebeiner cross-country skiers, left atrial dilatation was identified as a marker for AF [94], but as AF itself might cause atrial dilatation, a causal relationship between atrial remodeling and AF in veteran skiers has not been established. Myocardial edema and inflammation after endurance exercise or competitions have been suggested as underlying mechanisms for myocardial fibrosis in athletes [176, 177].

Finally, the autonomic nervous system seems to play a role in the etiology of atrial arrhythmias in athletes. Endurance sport practice is associated with vagal or parasympathetic pre-dominance with low resting heart rates [178]. A high vagal tone might facilitate macro re-entry circuits in the atria by shortening of the atrial refractory period [138, 156], and low heart rates predict AF in men [162]. In a recently published animal study, prolonged endurance exercise was associated with an increased sensitivity to cholinergic stimulation in atrial cardio myocyte potassium channels, that seemed to be mediated through mRNA (messenger Ribonucleic acid) down-regulation of potassium-channel-inhibiting RGS (Regulators of G-protein signaling) proteins [179]. This study supports that enhanced vagal activity plays a central role in the pathophysiology of AF in endurance-trained individuals.

7 Conclusions

1. Endurance sport practice seemed to be a risk factor for AF in men aged ≥65 years.

2. Years of regular endurance exercise were associated with a gradually increased risk of both AF and AFL in men.

3. Prolonged endurance exercise might be associated with an increased risk of AF also in women.

4. AF was associated with poor subjective health, but the vast majority of veteran athletes engaged in regular PA and endurance exercise also after the onset of AF.

8 Consequences of this thesis and suggestions for future research

8.1 Consequences of this thesis

This thesis suggests that endurance sport practice and prolonged endurance exercise is associated with an increased risk of AF in men. It demonstrates that AF is prevalent also among female veteran athletes and indicates that prolonged endurance exercise might be associated with the risk of AF also in women.

The literature suggests a complex association between PA, exercise and AF: For the vast majority of the general population, regular PA and exercise probably reduce the risk of AF [109, 116, 141, 142, 171]. On the other hand, this thesis indicates that prolonged and regular endurance exercise might increase the risk of AF gradually on the upper end of the activity range.

It might be reasonable to inform veteran athletes about a possible increased risk of AF, also in the absence of established AF risk factors. At the same time, this thesis has demonstrated that AF do not prevent the majority of veteran athletes from profiting from the benefits of regular PA and exercise. This result supports that, despite a possible increased risk of AF by prolonged endurance exercise, general exercise restrictions should be avoided. Such restrictions could prevent individuals from taking advantage of the health promoting effects of PA and have adverse implications on a public health level [116, 180].

Our current knowledge depends almost exclusively on observational studies, and many questions regarding the duration, intensity and type of exercise that might increase the risk of AF still remain unanswered. Meanwhile, the benefits of regular PA and exercise should be enhanced, and health care workers should recognize their strong responsibility to encourage individuals of all ages to engage in regular PA and exercise.

8.2 Suggestions for future research

Future studies of the association between endurance exercise and sport practice and the risk of AF should be prospective with a long follow-up period, include individuals across a broad range of exposure in order to investigate the optimal dose of exercise [129, 180], assess possible confounding factors and include both men and women. Furthermore, future research should focus on determining underlying mechanisms in the association between exercise and AF and include cardiac imaging, biomarkers of inflammation and myocardial fibrosis and electrophysiological studies. Furthermore, they should investigate long-term consequences of AF in veteran athletes. Future studies should include different subtypes of AF, individuals with different stroke risk profiles, record co-morbid conditions and OAC and investigate the natural course of AF in athletes, incidence of stroke, heart failure, death and other cardiovascular endpoints.

The participation in endurance sports events has increased, also among women. In this thesis we have demonstrated very high attendance rates in two study populations of veteran athletes. Events with shorter distances than marathons and long-distance cross-country ski races are likely to attract more women, but also men that are less exposed to endurance exercise than participants in long-distance endurance events. Therefore, in order to gain a high attendance, a broad range of exposure and a sufficient number of female study participants, the use of participation lists from different endurance sports events might be a feasible method to recruit participants to further studies. Dependent on the study size and resources, health outcomes might be registered by self-reports, ECGs or national health registers, and outcome measurements should be validated, for instance by using handheld recording devices.

9 References

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10 Papers